IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:

Heal et al — Art Unit: 1614

Serial Number: 09/212,249 — Examiner: JONES

Filed: December 16, 1998

For: THERAPEUTIC AGENTS

RULE 132 DECLARATION

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir,

I, David John HEAL, a British Subject of Knoll Limited, St Nicholas Court, 25-27 Castle Gate, Nottingham, England, declare that:-

1) I am familiar with the subject matter of the subject application and have read the Official Action on the above case which was mailed on December 17, 1999.

2) My abbreviated Curriculum Vitae is appended below.

Name:	DAVID JOHN HEAL	
University Education:		London University.
College:		Chelsea College.
Degrees:	1971	BSc Biochemistry/Chemistry II:1 Honours.
	1972	MSc Analytical Chemistry.
	1978	PhD Biochemistry. Examiners: Dr L L Iversen Professor G Curzon
College:		King's College.
	1998	DSc Pharmacology
Employment:	1973 - 1975	Graduate Technician at MRC Clinical Pharmacology Unit, Oxford.
	1975 - 1980	Research Officer at the above Unit.
	1980 - 1986	Senior Research Officer at the above Unit.
	1986 - 1990	Section Leader Antidepressant Research and Neurochemical Methods Development at Boots Pharmaceuticals Research Department.
	1990 - 1995	Senior Section Leader, Mental Illness Projects at Boots Pharmaceuticals Research Department.
	1995 -1999	Head of CNS Biology at Knoll Pharmaceuticals Research and Development.
	1999 to date	Head of Obesity Biology at Knoll Pharmaceuticals Research now Knoll Limited
University Appointments:	1978 - 1981	Associate Lecturer in Biochemistry, Chelsea College, London University.
	1979 - 1981	Member of University of London Examinations Board.
	1979 - 1986	University of Oxford Supervisor in Physiological Sciences.
	1984 - 1986	University of Oxford Tutor in Pharmacology.
	1988 - 1991	Committee member of The Nottingham Neuroscience Group.
	1995 -	Honorary Senior Lecturer, University College, London.

Membership of Scientific Societies:	1982 -	Member of British Pharmacological Society.
	1986 -	Founder member of the Serotonin Club.
	1990 -	Member of the British Neuroscience Association.
	1995 -	Member of the American Society for Neuroscience.
Editorial Responsibilities:	1987 -	Editorial Board of Psychopharmacology.
	1988 -	Editorial Board of Neuropharmacology.
	1996 -	Editorial Board of British Journal of Pharmacology.

Books

Heal DJ and Marsden CA. (Eds). "The Pharmacology of Noradrenaline in the Central Nervous System" Oxford University Press, Oxford, 1990.

Marsden CA and Heal DJ. (Eds). "Central Serotonin Receptors and Psychotropic Drugs" Blackwell Scientific Publications, Oxford, 1992.

Elliott JM, Heal DJ and Marsden CA. (Eds). "Experimental Approaches to Anxiety and Depression". John Wiley, Chichester, 1992.

Full Papers and Book Chapters.

Over 110 paper published in scientific journals and books.

Abstracts

Over 200 communications and invited lectures given at national and international scientific meetings.

3) The studies on feeding and body weight described below were carried out under my supervision and control.

4) Individually-housed male Sprague-Dawley rats (Charles River, Kent) were maintained on reverse-phase lighting (lights off 10.00 - 18.00h) with free access to a moderately high-fat, powdered diet (normal rodent diet containing 20% lard; 39% of energy as fat) and tap water. Animals were acclimatised to these conditions for at least two weeks before experimentation. Rats were then weighed and randomly allocated into four weight-matched treatment groups (body weights in the range 320-430g at the start of the experiment).

After a three day baseline period, during which all the animals were dosed orally with vehicle, animals were given either vehicle po (n=8); sibutramine 3 mg/kg po (n=8) or orlistat 20 mg/kg po bid (n=8). These three groups of animals had free access to the high-fat diet. A second group of animals (n=8) was treated with orlistat (20 mg/kg po bid) but pair-fed with the sibutramine-treated group, ie these animals were given the amount of food eaten by the sibutramine-treated group in the previous 24 h. Body weights and 24 h food intakes were measured every day during the baseline period and for the 5 days of the study. Sibutramine hydrochloride was dissolved in de-ionised water. Orlistat was suspended in 5% gum arabic solution. Sibutramine was dosed at the onset of the dark period (10.00 h). Orlistat was dosed at the onset of the dark period and 6 h later. Statistical comparisons between the body weights and food intakes of the different treatment groups were made by analysis of co-variance followed by the multiple t-test.

5) Conclusions

It is evident from the data shown in Figure 1 that the weight-loss of rats receiving orlistat treatment is very small and, in addition, it fails to reach statistical significance. This result resembles the observation in man whereby clinical trials demonstrate that the additional effect of orlistat on bodyweight is relatively small (approximately 3% at maximum clinical dose of 120mg three times daily) when the placebo-treated weight reduction is subtracted (Finer et al, 2000, Int. J. Obes., 24, 306-313). The poor weight-loss with orlistat observed in our preclinical study occurs in spite of the fact that this treatment regime significantly reduces fat absorption indicating marked inhibition of intestinal lipase (Table 1). The probable explanation for the limited efficacy oforlistat is that the reduction in calorie intake produced by orlistat's inhibition of intestinal lipase is off-set by a compensatory increase in the rats' food intake (Figure 2). This is because orlistat's action which is exclusively within the alimentary tract precludes any effect of this drug to restrict food intake via either peripheral or central control mechanisms. In contrast, sibutramine which reduces food intake by increasing the hypothalamic satiety response (the feeling of fullness that leads to the termination of feeding) evokes a marked and sustained reduction in bodyweight of rats that is associated with significant reductions of food intake (Figures 1 and 2). Again, these experimental studies are consistent with human data from clinical trials which demonstrate that sibutramine produces much greater placebo-subtracted weight-loss (approximately 7% at maximum

clinical dose of 20mg daily; Bray et al, 1999, Obes. Res.,7,189-198) than orlistat (Finer et al, 2000). The experiment where orlistat is given to rats pair-fed to the same level of food intake as sibutramine-treated animals indicates that sibutramine's hypothalamic action to decrease food intake could be predicted to release the full potential of orlistat's lipase inhibitory actions as shown in Figure 1. This conclusion is evidenced by the profound weight-loss observed for the pair-fed-orlistat group which is significantly greater than that of either sibutramine or orlistat when given alone. In fact, this experimental result leads to the conclusion that in the clinic there is the potential for a synergistic interaction between these two weight-loss agents to reduce bodyweight beyond the levels that would be predicted from a simple addition of their respective weight reducing effects.

I, David John HEAL, the undersigned declarant, declare further that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, of Title 18 of the United States Code, and that such wilful false statements may jeopardise the validity of the application or any patent issuing thereon.

David John HEAL _____

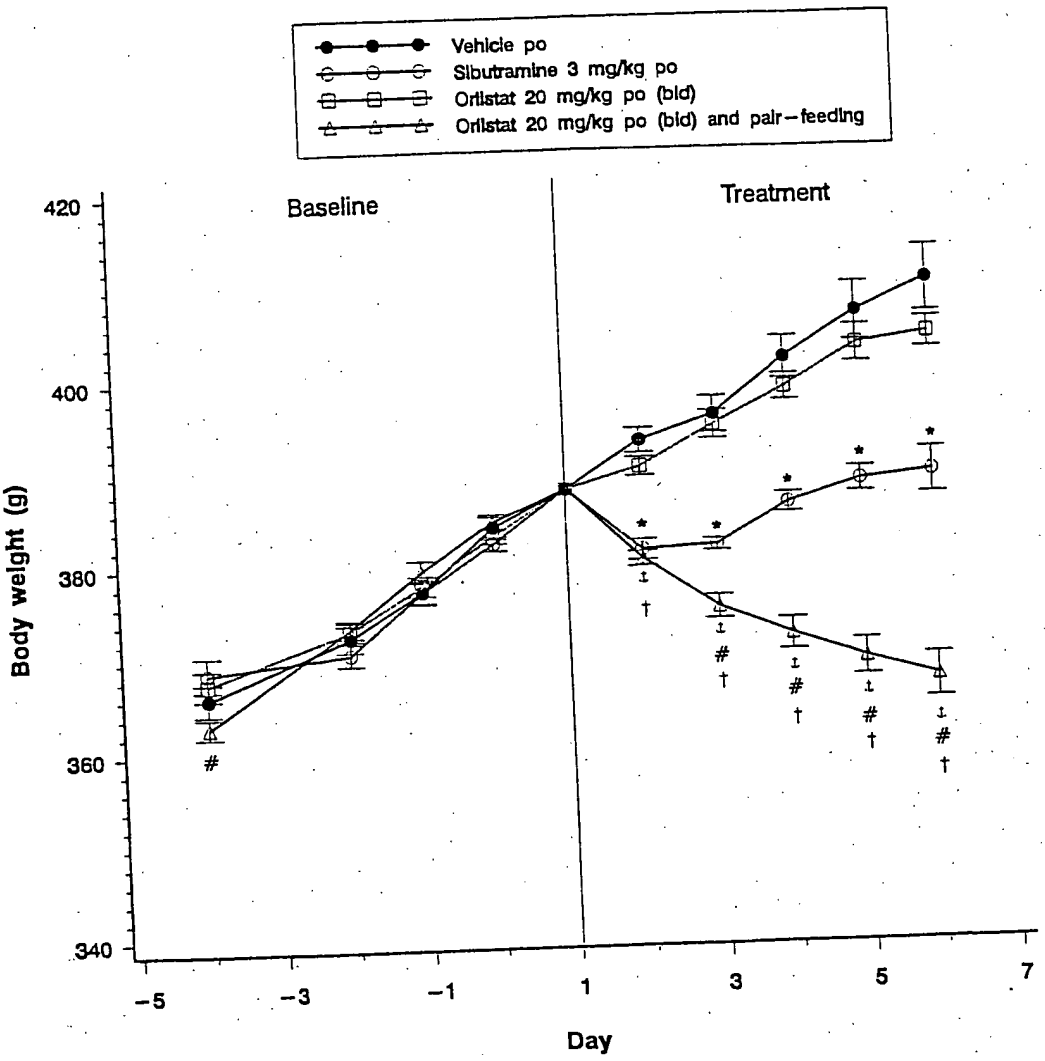
Signed at Nottingham, England on the 19 day of JUNE 2000.

Table 1 Effect of orlistat on absorption of ingested dietary fat

Treatment		n	Mean fat in diet lost (%)	SEM	p
Day 1					
Control		10	3.0	0.22	
Orlistat	10 mg/kg bid	10	12.1	1.33	<0.001
Orlistat	20 mg/kg bid	10	19.8	2.43	<0.001
Day 8					
Control		10	2.8	0.15	
Orlistat	10 mg/kg bid	10	12.5	1.32	<0.001
Orlistat	20 mg/kg bid	10	31.1	2.71	<0.001
Day 15					
Control		10	2.7	0.39	
Orlistat	10 mg/kg bid	10	13.5	1.20	<0.001
Orlistat	20 mg/kg bid	10	31.7	1.90	<0.001

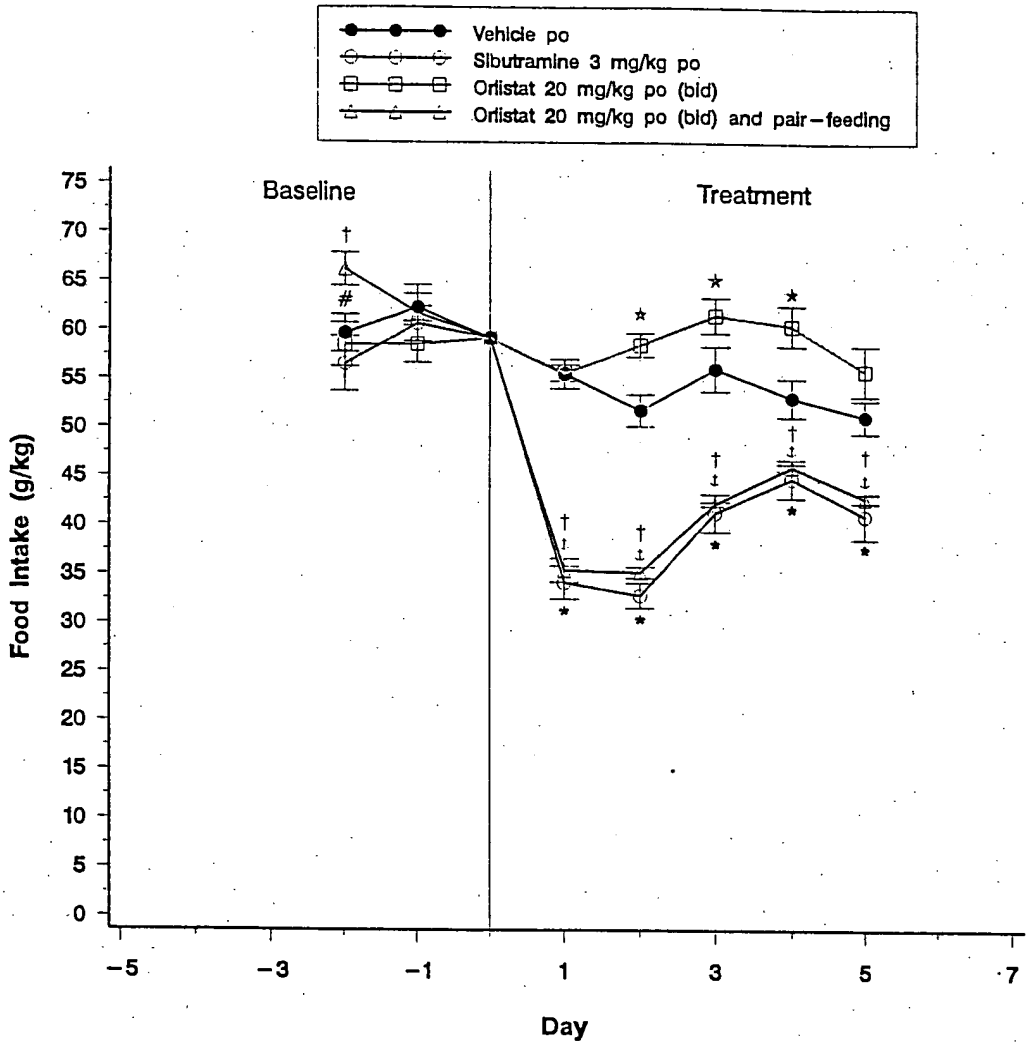
Faecal samples were collected over 24 h and their fat content determined. Results are expressed as % fat lost in the faeces related to total fat consumed during the same 24 h period.

Figure 1 **Effect of orlistat on body weight in rats pair-fed with a sibutramine-treated group**



Results are expressed as means ± SEM of residuals
n=8
* $p<0.05$ Sibutramine 3 mg/kg vs vehicle
↕ $p<0.05$ Orlistat 20 mg/kg (pair-fed) vs vehicle
† $p<0.05$ Orlistat 20 mg/kg (pair-fed) vs Orlistat 20 mg/kg
# $p<0.05$ Orlistat 20 mg/kg (pair-fed) vs Sibutramine 3 mg/kg

Figure 2 Effect of orlistat on food intake in rats pair-fed with a sibutramine-treated group



Results are expressed as means ± SEM of residuals
n=8
* $p<0.05$ Sibutramine 3 mg/kg vs vehicle
★ $p<0.05$ Orlistat 20 mg/kg vs vehicle
↕ $p<0.05$ Orlistat 20 mg/kg (pair−fed) vs vehicle
† $p<0.05$ Orlistat 20 mg/kg (pair−fed) vs Orlistat 20 mg/kg
# $p<0.05$ Orlistat 20 mg/kg (pair−fed) vs Sibutramine 3 mg/kg